REMARKS

Claims 42-51 are pending. The specification has been amended to correct an obvious typographical error. Support for this amendment can be found on page 130, Example 15, which pertains to quantitative expression analysis and particularly at page 148, Section I, entitled "Clone 16467945" pertaining to the relative tissue expression analysis for the claimed polynucleotide. No new matter has been added.

Rejections under 35 U.S.C. §101

The Examiner has rejected claims 42-51 under 35 U.S.C.§101, as allegedly lacking a specific, substantial, asserted utility. Specifically, the Examiner states that the claimed "nucleic acids encode proteins that are described as useful as novel members of protein families due to the presence of domains and sequence relatedness." The Examiner contends that the disclosure does not identify the protein families, or the function of such protein family. The Examiner further contends that there is no specific disease or specific function that is suggested by the limited homology. The Examiner states that: "Tissue specific expression does not rely on specific properties or functions of the encoded protein," and that the specification lists several pages of expression levels in several tissues, which indicate that the probe is not tissue specific. The Examiner alleges that the specification doesn't disclose any diseases or conditions known to be associated with the encoded protein. Finally, the Examiner contends that the Applicants' previous response is not persuasive, stating "applicants assertion of the utility regarding the above diseases is not substantial as the specification does not disclose any evidence to support the assertion. Thus, the asserted utility has not been presented in mature form and the rejection remain."

Applicants respectfully disagree. The MPEP 2107, II(B)(1) states:

> "If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

The specification states:

> "Experimental results presented in Example 16 show that, relative to cells from normal tissues, the proteins encoded by Clone 16467945.0.85 (PROX 16) and Clone 16467945.0.88 (PROX 17) are highly over-expressed in certain breast cancer cell lines, ovarian cancer cell lines, renal cancer cell lines, and colon cancer cell lines. In addition, the encoded proteins are strongly suppressed in lung cancer cell lines in comparison with normal lung cells. These results suggest that this clone may be used as a selective probe for detection or diagnosis of these cancers..." (See page 56, last paragraph to top of page 57, emphasis added.)

As stated in Applicants' response (filed September 8, 2003) to the previous Office Action (dated May 7, 2003), at least one substantial and specific utility exists for the claimed invention and is readily apparent based on the teachings of the specification. In that response the Examiner's attention was invited to Example 15, which provides specific teaching of methods, by which, one of skill in the art, could measure the expression levels of a PROX-encoding nucleic acid in a biological sample, and particularly, to pages 148-150 of the specification disclosing the results of this assay for the claimed SEQ ID NO:33. Applicants acknowledge the Examiner's statement "The results are said to be presented in Example 16." (page 5 of Office Action dated December 9, 2003). Applicants have corrected this obvious typographical error, in the specification, herein, to recite, "Experimental results presented in Example 15 show that...". Applicants respectfully submit that there is clearly an asserted utility set forth in the specification.

> The MPEP, 2107, II. (B)(1)(i) states:
>
> "A claimed invention must have a specific and substantial utility. This requirement excludes "throw-away, " "insubstantial," or "nonspecific" utilities, such as the use of a complex invention as landfill, as a way of satisfying the utility requirement of 35 U.S.C. 101."

The asserted utility for the claimed invention is not a "throw-away," "insubstantial," or "nonspecific" utility. Applicants respectfully submit the use of the polynucleotide SEQ ID NO:33 to detect or differentiate cancerous tissue, specifically breast, ovarian, renal, colon, and lung cancers, utilizing an expression assay, is taught and is exemplified in the specification and clearly constitutes a specific utility. Furthermore the asserted utility is not: a basic research tool; intended for an unspecified disease; an assay for identifying a material that itself has no utility; a method for making a material that has no utility; or an intermediate product to a final product

that has no utility. Applicants respectfully submit the asserted utility is a substantial utility with a real world use.

The Examiner's contention that the claimed invention lacks utility because allegedly: it is described as useful as a novel, homologous, member of an unidentified protein family; and no specific disease or specific function is suggested by the limited homology, is moot as the specification asserts a supported utility that is not based upon homology. The Examiner's contention that the claimed invention lacks utility because: "Tissue specific expression does not rely on specific properties or functions of the *encoded protein*"(emphasis added); and the specification doesn't disclose any diseases or conditions known to be associated with the *encoded protein*; are irrelevant as these elements of the protein are not required in order to demonstrate a utility for the claimed polynucleotide.

Furthermore, the Examiner's contention that the specification lists several pages of expression levels in several tissues, which indicates that the probe is not tissue specific is irrelevant as the expression of the claimed invention, SEQ ID NO:33 need not be detected in very few or a select tissue to have utility. Applicants respectfully submit that if the gene is shown to have a *differential* expression among tissues, that provides useful, actionable information then the utility requirement is satisfied. The Examiner's attention is invited to Table 38 (page 148-150) in the specification disclosing that the relative expression of PROX17 is detected at: 2.94% in normal colon tissue, compared to elevated expression detected in the majority of colon cancers tested (13.33%, 21.94%, 18.32%, 5.13%): 12.37% in normal kidney tissue, compared to elevated expression in renal cancer ACHN (70.06%): 7.04% in normal mammary gland, compared to elevated expression in breast cancer MCF-7 (100%) and in T47D (26.53%): and 3.51% in ovarian tissue compared to elevated expression in ovarian cancer IGROV-1 (22.2%) and in SK-OV-3 (11.13%). The specification teaches that in lung cancer, relative expression of PROX17 is decreased in 10 specimens tested (ranging from 0% to 13.15%) compared to normal lung tissue (21.48%). Therefore one of skill in the art would appreciate that the polynucleotide SEQ ID NO:33, encoding SEQ ID NO:34 is differentially expressed in certain malignant cells compared to normal tissue counterparts, and therefore may be used to aid in differentiating malignant tissues from normal tissues.

Finally, the Examiner's contends that the "applicants assertion of the utility regarding the above diseases is not substantial as the specification does not disclose any evidence to support the assertion." The Examiner also contends that Applicants' Amendment and Response to May 7, 2003 Office Action, dated September 8, 2003 (herein referred to as "previous response") with regards to the rejection under 35 U.S.C. §101, is not persuasive. The Examiner states that the Applicants contend the claimed invention has at least one substantial and specific utility and points to the use of the DNA in diagnostic applications involving cancer. The Examiner finds this not persuasive as allegedly: (a) "applicants assertion of the utility regarding the above diseases is not substantial as the specification does not disclose any evidence to support the assertion. Thus, the asserted utility has not been presented in mature form and the rejection remain"; (b) " there is no evidence or example that the PROX17 is not expressed in healthy tissues"; (c) no indication of how to develop a drug and significant further experimentation would be required to identify patients and course of treatment; and d) expression of DNA does not equate to expression of protein.

Applicants disagree.

A. Utility of Claimed Invention is Supported in the Specification.

In addition to the discussion above, the Examiner's attention is invited to the previous response, page 6, second to last paragraph which states:

> "...Example 15, provides specific methods for detecting PROX gene expression and specifically shows that SEQ ID NO:33 expression levels differentiate cancer specimens from their normal counterparts...";

and further at page 7, last paragraph:

> "...As discussed *supra*, the expression analysis results of SEQ ID NO:33 presented in Example 15 shows that SEQ ID NO:33 is over expressed in breast, ovarian, renal and colon cancer tissue when compared to corresponding normal tissues...".

Applicants respectfully submit that clearly the specification discloses evidence, and exemplifies Applicants' assertion of utility.

B. Evidence for Differential Expression of PROX17

As discussed above, the claimed invention, polynucleotide SEQ ID NO:33 encoding polypeptide SEQ ID NO:34 clearly shows a differential expression pattern that is particularly evident in malignant tissues compared to normal counterparts. Evidence of lack of expression, or reduced relative expression in healthy tissues is demonstrated in colon, kidney, ovary and mammary gland allowing for the differential expression to be demonstrated in malignant cells originating from these tissues. As taught in the specification and furthermore appreciated by the Examiner (page 5 of the December 9, 2003 Office Action), the gene is suppressed in lung cancer compared to normal tissue, so that it is the expression of the gene in healthy tissue that is useful and provides for a differential to be found and malignant lung to be detected (see Example 15).

C. Drug Development

The pending claims pertain to the polynucleotide SEQ ID NO:33 encoding the polypeptide SEQ ID NO:34. The subject matter of the pending claims is supported by a specific and substantial utility as described above and is sufficient for patentability of the pending claims. Claims pertaining to drug development are encompassed by non-elected Groups VI-XIII as defined by the Examiner in the Restriction Requirement dated October 1, 2002. As such, the Examiner's point is irrelevant to the claims currently under examination.

D. Protein Expression

While PROX17 protein expression is demonstrated in Example 14, page 130 in the specification, the pending claims pertain to the polynucleotide SEQ ID NO:33 encoding the polypeptide SEQ ID NO:34. Claims pertaining to the protein are encompassed by non-elected Group I as defined by the Examiner in the Restriction Requirement dated October 1, 2002. As such, the Examiner's point is irrelevant to the claims currently under examination.

Thus the claimed invention is supported by a specific and substantial utility and the rejection under 35 U.S.C. §101 should be withdrawn.

Rejections under 35 U.S.C. §112, first paragraph

Claims 42-51 are rejected under 35 U.S.C. 112, first paragraph as: (a) allegedly not supported by a substantial asserted utility and therefore one of skill in the art would not know how to use the claimed invention without undue experimentation; and (b) as containing subject matter which allegedly was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed and lacking written description.

Applicants respectfully disagree.

A. Claims are supported by an asserted utility

As described above, at least one substantial and specific utility exists for the claimed invention and is readily apparent based on the teachings of the specification. The use of the polynucleotide SEQ ID NO:33 to detect or differentiate cancerous tissue, specifically breast, ovarian, renal, colon and lung cancers, utilizing an expression assay, is taught and is exemplified in the specification and clearly constitutes a specific utility. One of skill in the art would appreciate that the polynucleotide SEQ ID NO:33 encoding SEQ ID NO:34 is differentially expressed in certain malignant cells compared to normal tissue counterparts and therefore may be used in differentiating malignant tissues from normal tissues. Applicants submit that the asserted utility is a substantial utility with a real world use. Thus, the claimed invention is supported by an asserted, specific, and substantial utility; therefore this rejection should be withdrawn.

B. Inventor was in possession of claimed invention and has provided sufficient written description.

The Examiner contends that the specification (page 2) states that the invention pertains to nucleic acids and secreted polypeptides encoded thereby, fragments, homologs, analogs and derivatives thereof, referred to as PROX, but that there is no definition of PROX.

Applicants disagree. The Examiner's attention is invited to page 5 of the specification, which states:

> "The invention includes 18 PROX nucleic acids, PROX polypeptides, PROX antibodies, or compound or methods *based on these nucleic acids*. These nucleic acids, and their associated polypeptides, antibodies and other compositions are referred to as PRO1, PRO2, PRO3...through PRO17, respectively. These sequences are collectively referred to as "PROX nucleic acids or "PROX" polynucleotides" (where X is an integer between 1 and 17) and the corresponding encoded polypeptide is referred to as a "PROX polypeptide" or "PROX protein."

Furthermore Table 1 (pages 5 and 6) provides a cross-reference between: 1) an inventor-designated clone number; 2) a PROX number for reference in the specification; 3) a table number disclosing the nucleic acid and amino acid sequence information; and 4) corresponding SEQ ID NOS. Applicants respectfully submit that an applicant is allowed to be their own lexicographer and has chosen a term "PROX" combined with an integer between 1-17, for the 17 clones disclosed in the specification to simplify reference to each specific clone "PROX" 1-17, or collectively "PROX" polynucleotides or "PROX" polypeptides in the specification. Thus "PROX" and its use throughout the specification is clear. Furthermore, this choice of terms by the Applicants should not invoke the Examiner's contention that the claimed invention was not described in the specification to reasonably convey that the inventor(s) were in possession of the claimed invention at the time of filing or a written description rejection. In fact, it is quite clear from the specification that the Applicants were in position of at least 17 novel clones, PROX 1-17 at the time of filing. The rejection should be withdrawn.

The Examiner contends that the specification (page 4) states methods are provided to treat or prevent or delay a PROX-associated disorder or proliferation-associated disorder but that no specific disease or disorder is described or exemplified.

Applicants disagree and respectfully submit that the pending claims pertain to the polynucleotide SEQ ID NO:33 encoding the polypeptide SEQ ID NO:34. Claims to methods of

treatment, prevention or delay of a disease or disorder are encompassed by non-elected Groups IX, X, XI and XIII as defined by the Examiner in the Restriction Requirement dated October 1, 2002. As such, the Examiner's point is irrelevant to the claims currently under examination and the rejection should be withdrawn.

The Examiner further contends that the specification (page 6) states PROX nucleic acids and polypeptides are useful as novel members of protein families according to the presence of domains and sequence relatedness to previously described proteins but that the specification does not demonstrate or describe any protein in association with the claimed invention.

Applicants disagree and respectfully invite the Examiner's attention to the claimed invention, the polynucleotide SEQ ID NO:33 which encodes the polypeptide SEQ ID NO:34 is described in the specification, specifically in Table 18, pages 54-56. A BLASTP and BASTX analysis is described at page 56, immediately after Table 18. Thus the Examiner's point is not relevant to the rejection under 35 U.S.C. 112, first paragraph as allegedly not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed nor is it relevant to a lack of written description rejection. The rejection should be withdrawn.

The Examiner further contends that the specification states PROX nucleic acids and polypeptides can be used to identify cell types based on the presence or absence of PROX nucleic acids, but that tables show a broad spectrum of tissue types, "thus specificity is lacking."

Applicants disagree and respectfully invite the Examiner's attention to Section I. Entitled "Clone 16467945" at page 148, including Table 38, page 148-150 disclosing relative expression results for this clone, which are further described at page 56, last paragraph. Contrary to the Examiner's statement, it is appropriate to determine the gene expression level in numerous tissues and report the data. Just because the table contains a broad spectrum of tissues that does not mean "specificity is lacking." With specific regards to PROX17 gene expression reported in the table, one of skill in the art would know that it is not reasonable to expect a particular gene to be expressed in only one tissue type, this is found only very rarely, if at all. Instead, as taught in

the specification, those skilled in the art would know to evaluate the data in terms of detected *relative* expression of the gene in the different tissues.

> "Results were recorded as CT values (cycle at which a given sample crosses a threshold level of fluorescence) using a logarithmic scale. The difference in RNA concentration between a given sample and the sample with the lowest CT value was represented as 2 to the power delta CT (*i.e.*,$2^{\delta CT}$). The percent relative expression was then obtained by taking the reciprocal of this RNA difference and multiplying by 100." (page 131)

As described above and in the specification, this gene does show differential tissue expression indicating an association with cancerous tissues (colon:colon cancer, 2.94:21.94%; kidney:renal cancer, 12.37:70.06%; mammary gland:breast cancer 7.04:100%; ovary:ovarian cancer, 3.51:22.2%; and lung:lung cancer, 21.48:0%). Thus the Examiner's statement that specificity is lacking is not supported and furthermore, the Examiner's point is not relevant to the rejection under 35 U.S.C. 112, first paragraph as allegedly not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed, or a written description rejection. In fact, the claimed polynucleotide SEQ ID NO:33 which encodes the polypeptide SEQ ID NO:34 is shown to have been isolated and the differential tissue expression exemplified in the specification as filed.

The Examiner states that pages 56-57 disclose Clone 16467945.0.88 (PROX 17), that is highly over expressed in certain breast, ovarian, renal, and colon cancer cell lines and that the encoded protein is suppressed in lung cancer, and that the clone may be used as a selective probe for detection or diagnosis of these cancers, results are said to be in Example 16. Example 16 (pages 150-151) however refers to Clone 11692010.0.51, PRO3.

Applicants disagree and respectfully submits that this is a typographical error and the Examiner's attention is invited to Example 15, Quantitative Analysis of the Tissue Distribution of Expression of PROX Nucleic Acids, pages 130-150, particularly Section I, Clone 16467945, page 148-150. The specification has been amended herein to correct this error. The differential expression of the claimed invention polynucleotide SEQ ID NO:33 encoding polypeptide SEQ ID NO:34 is present in the specification as filed. Thus Applicants submit that the invention was

certainly in- hand at the time of filing and 35 U.S.C. §112, first paragraph, possession of the invention at the time of filing and written description rejections should be withdrawn.

The Examiner contends that the claims are directed to a nucleic acid and encoded protein, but that the specification has "no indicia as to bio activity of the protein per se", and there is no "analogous art".

Applicants disagree and respectfully submits that the claims are directed to a nucleic acid SEQ ID NO:33 *encoding* a protein SEQ ID NO:34. What is required for patentability is that the claimed invention be novel, nonobvious and useful. It is not required that an applicant demonstrate a naturally occurring activity such as a "bio activity" nor an activity the Examiner defines. It *is* required that the applicant knows and describes a use for the invention. Furthermore the protein *per se* is not the subject of the claims and in fact is the subject matter of a non-elected Group I restricted by the Examiner. Therefore the Examiner's contention is not relevant to the pending claims nor to the rejection under 35 U.S.C. 112, first paragraph. The rejection should be withdrawn.

The Examiner states that the specification (page 93) indicates nucleic acid molecules, proteins, etc, can be used in the following methods: screening assays, detection assays, predictive medicine, and methods of treatment, but that no standardized screening assay is demonstrated and there is no demonstration of specific detection assays or any methods of treatment in association with a specific disease or disorder.

Applicants disagree. A specific assay is described in Example 15, Quantitative Analysis of the Tissue Distribution of Expression of PROX Nucleic Acids, pages 130-150, particularly Section I, page 148-150 describes the assay results for Clone 16467945, PROX17, SEQ ID NO:33. RNA isolated from cell and tissue samples was converted to cDNA, which was then subject to real-time quantitative PCR analysis using commercially available reagents, described on pages 131-132. Therefore a detection assay is described and exemplified in the specification as filed. Furthermore, pending claims pertain to a nucleic acid SEQ ID NO:33 encoding a protein SEQ ID NO:34. Claims to methods: screening assays, detection assays, predictive

medicine, and methods of treatment, are currently not pending as they are non-elected Groups IV, V, VI, VII, VIII, IX, X, XI, and XIII as defined in the restriction requirement imposed by the Examiner. Therefore the Examiner's contention is irrelevant to the pending claims. The rejection should be withdrawn.

The Examiner further contends that the specification at page 132+ and Tables 22 and 23 provide primer sequence information and relative expression results for clones that are highly expressed in certain tissues but that the specification does not provide evidence of expression of claimed polypeptide as the expression of the polynucleotides does not unequivocally mean expression of the polypeptides. The Examiner further states that pages 133-150 lists all kinds of tissues and expression levels, thus it appears that expression is not tissue specific.

Applicants disagree. The pending claims pertain to the PROX17 polynucleotide that encodes the polypeptide. Claims to the polypeptide are not currently pending as they are non-elected Group I subject to restriction by the Examiner. With regards to tissue specificity, as described above (see page 6 and pages 11-12), one of skill in the art would not expect to see single tissue specificity but would recognize from the relative differential expression, the association of PROX17 expression with certain malignant tissues. The Applicants respectfully submit that the Examiner's point is moot with regards to a 35 U.S.C. §112 possession of the invention at the time of filing and written description rejection. The rejection should be withdrawn.

The Examiner states: "Thus, absent data as to use of encoded protein and a showing of a probe that is tissue specific, one of skill in the art would have to engage in undue experimentation" (emphasis added).

Applicants strongly disagree. The pending claims pertain to the polynucleotide SEQ ID NO:33 encoding the polypeptide SEQ ID NO:34. Claims to the protein are not currently pending and data pertaining to the use of the protein is not relevant to the patentability of the pending polynucleotide claims. Further, as discussed above, the specification exemplifies a tissue

specificity with regards to the differential expression of SEQ ID NO:33. The rejection should be withdrawn.

The Examiner contends that the Applicants' comments in the previous response regarding the rejection under 35 U.S.C. 112, first paragraph (enablement) were not found to be persuasive due to: 1) large quantity of experimentation necessary to determine an activity or property of disclosed PROX17 and to determine how to use claimed invention; 2) lack of direction/guidance presented in the specification; 3) absence of working examples; 4) complex nature of the invention; 5) state of the prior art establishing biological activity cannot be predicted based on structural similarity; 6) claims fail to recite particular biological activity. The Examiner alleges that undue experimentation would be required.

Applicants disagree. A property or activity of PROX17 polynucleotide, for example, the tissue expression pattern is described and exemplified in the specification, particularly in Example 15. The specification teaches how to use PROX17 polynucleotide in an expression assay, which differentiates certain malignant from normal tissues. As described herein, clearly the specification has provided sufficient direction and guidance, as well as a working example in Example 15, in this regard. Applicants do not rely on homology of the claimed invention with known structures in order to define the invention or demonstrate a utility, therefore biological activity needn't be predicted based upon structural similarity and furthermore is not relevant to the pending claims. Applicants respectfully submit that undue experimentation is not required as the invention is fully described and its use exemplified, therefore fully enabled in the specification as file. The rejection should be withdrawn.

The Examiner further contends that the Applicants' comments regarding the rejection under 35 U.S.C. 112, first paragraph, written description, points to Example 15 and a showing that SEQ ID NO:33 is over expressed in breast, ovarian, renal and colon cancer tissue compared to normal tissues, is not persuasive, as it is not specific. Examiner contends that such can be done with any polynucleotide.

Applicants disagree and furthermore respectfully suggests that perhaps the Examiner intended this statement to be part of a 35 U.S.C. §101 rejection. Regardless, the relative expression pattern of each gene is unique and not any polynucleotide investigated in a quantitative expression analysis would provide the results shown in Table 38. Specifically polynucleotide PROX17 provides those results. For example, the Examiner's attention is invited to Tables 23, through 36, which show the relative expression pattern for 16 other PROX genes. No one-expression pattern is identical to any other. The expression pattern for PROX 17 is specific and the rejection whether it is under §112 or §101 should be withdrawn.

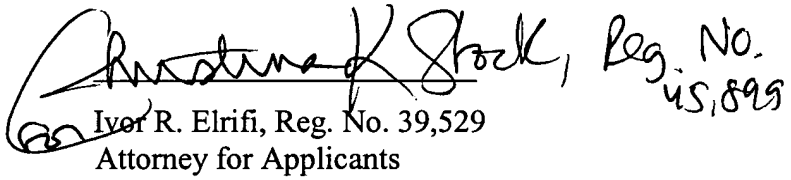
The Examiner contends, "The specification does not adequately describe the encoded protein or function. Therefore it appears that the claimed DNA encodes a non-functional protein." Further: "The specification fails to teach the skilled artisan how to use the claimed polynucleotide to make biologically active PROX-17 without resorting to undue experimentation to determine what the specific biological activities of the PROX-17 are."

Applicants disagree. The specification describes the protein at pages 54-56, Table 18. Applicants respectfully submit that there is no support for the Examiners contention that the claimed DNA encodes a non-functional protein. The specification exemplifies the use of the DNA to make PROX17 protein at page 130, Example 14. Furthermore the pending claims pertain to the polynucleotide SEQ ID NO:33 encoding the polypeptide SEQ ID NO:34. Claims to the polypeptide are not currently pending as they are subject of non-elected Group 1 as restricted by the Examiner. Therefore, the Examiner's contentions regarding the function or activity of the polypeptide are not relevant to the pending claims pertaining to the polynucleotide and the rejection should be withdrawn.

CONCLUSION

Applicants respectfully request that the amendments and remarks made herein be entered and made of record in the file history of the present application. Applicants respectfully submit that this paper is fully responsive and that the pending claims are in condition for allowance. Such action is respectfully requested. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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